QUALITY-OF-LIFE OUTCOMES AND SUBGROUP ANALYSIS IN A PHASE 3 RANDOMIZED STUDY OF ENSARTINIB VS CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE NSCLC PATIENTS: EXALT3

Wu Y,[1] Wang Z,[2] Wu G,[3] Poddubskaya E,[4] Mok T,[5] Reck M,[6] Chiappori A,[8] Lee DH,[9] Breder V,[10] Orlov S,[11] Cicin I,[12] Cheng Y,[13] Liu Y,[14] Fan Y,[15] Yen J,[16] Zhou J,[17] Liang C,[17] Mao L,[17] Selvaggi G,[17] Horn L,[18] Wakelee H[19]

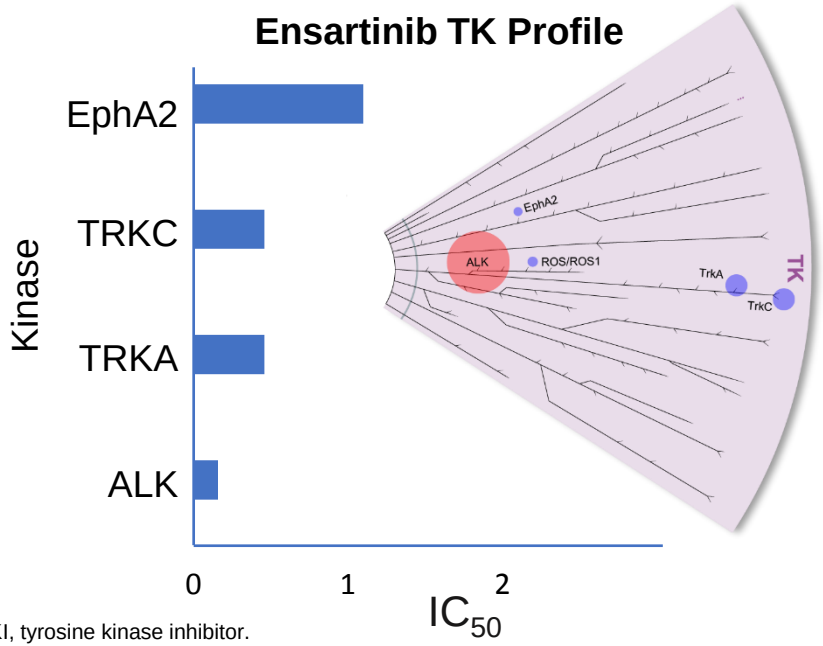
[1]Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; [2]Beijing Cancer Hospital, Beijing China; [3]Cancer Center of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [4]Sechenov University, Moscow, Russia; [5]The Chinese University of Hong Kong, Hong Kong, China; [6]LungClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [8]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Asan Medical Center, Seoul, South Korea; [10]Russian Cancer Research Center - Blokhin, Moscow, Russia; [11]Pavlov First Saint Petersburg State Medical University, St Petersburg, Russia; [12]Trakya University, Edirne, Turkey; [13]Jilin Cancer Hospital, Changchun, China; [14]The First Hospital of China Medical University, Shenyang, China; [15]Zhejiang Cancer Hospital, Hangzhou, China; [16] Guardant Health, Redwood City, CA, USA; [17]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA; [18]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [19]Stanford Cancer Institute, Stanford University, Stanford, CA, USA

DISCLOSURES

Commercial Interest	Relationship(s)
AstraZeneca, BI, BMS, Eli Lilly, MSD, Pfizer, Roche	Speakers bureau
AstraZeneca, BI, Novartis	Consultant
AstraZeneca, BMS, Pfizer	Contracted research

Introduction

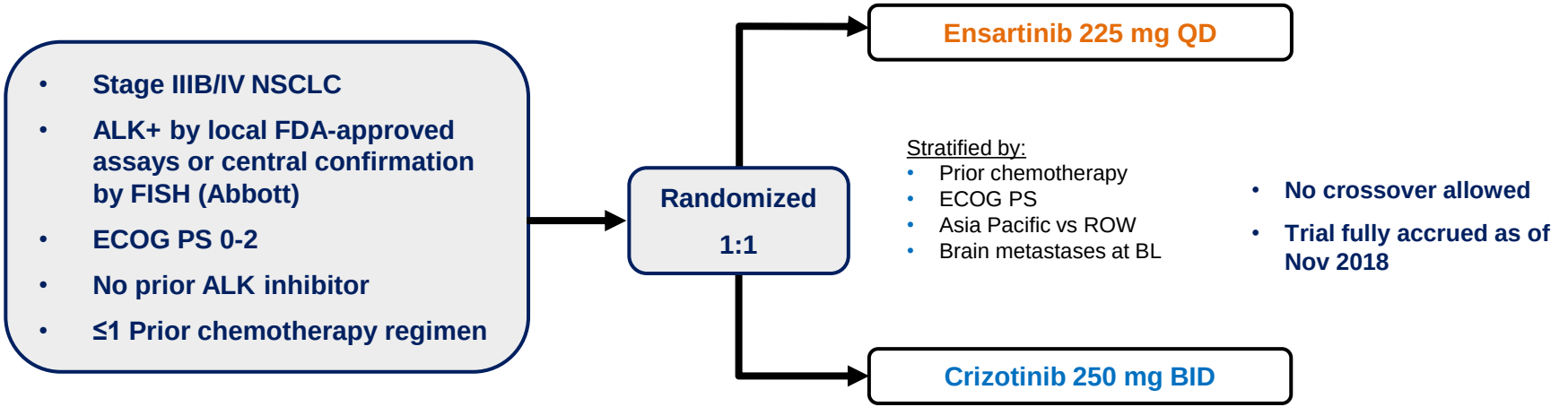
- Oncogenic rearrangements of the *ALK* gene occur in approximately 5%-7% of patients with NSCLC[1]
- Ensartinib is a potent, second-generation, once-daily oral ALK inhibitor, with broad preclinical activity against *ALK* resistance mutations[2]
  - Ensartinib potency is more than 10 times greater than that of crizotinib in enzymatic assays[2]
- In phase 1/2 trials, ensartinib has shown promising antitumor activity in patients with ALK TKI–naive, crizotinib-refractory, advanced *ALK*-positive NSCLC, including those with brain metastases[3-5]



ALK, anaplastic lymphoma kinase; IC_{50}, half maximal inhibitory concentration; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor.

1. Tsao AS, et al. *J Thorac Oncol.* 2016;11(5):613-638; 2. Lovly CM, et al. *Cancer Res.* 2011;71(14):4920-4931; 3. Horn L, et al. *Clin Cancer Res.* 2018;24(12):2771-2779; 4. Fang WF, et al. *J Clin Oncol.* 2018;36(Suppl 15):e21122; 5. Yang Y, et al. *Lancet Respir Med.* 2020;8(1):45-53.

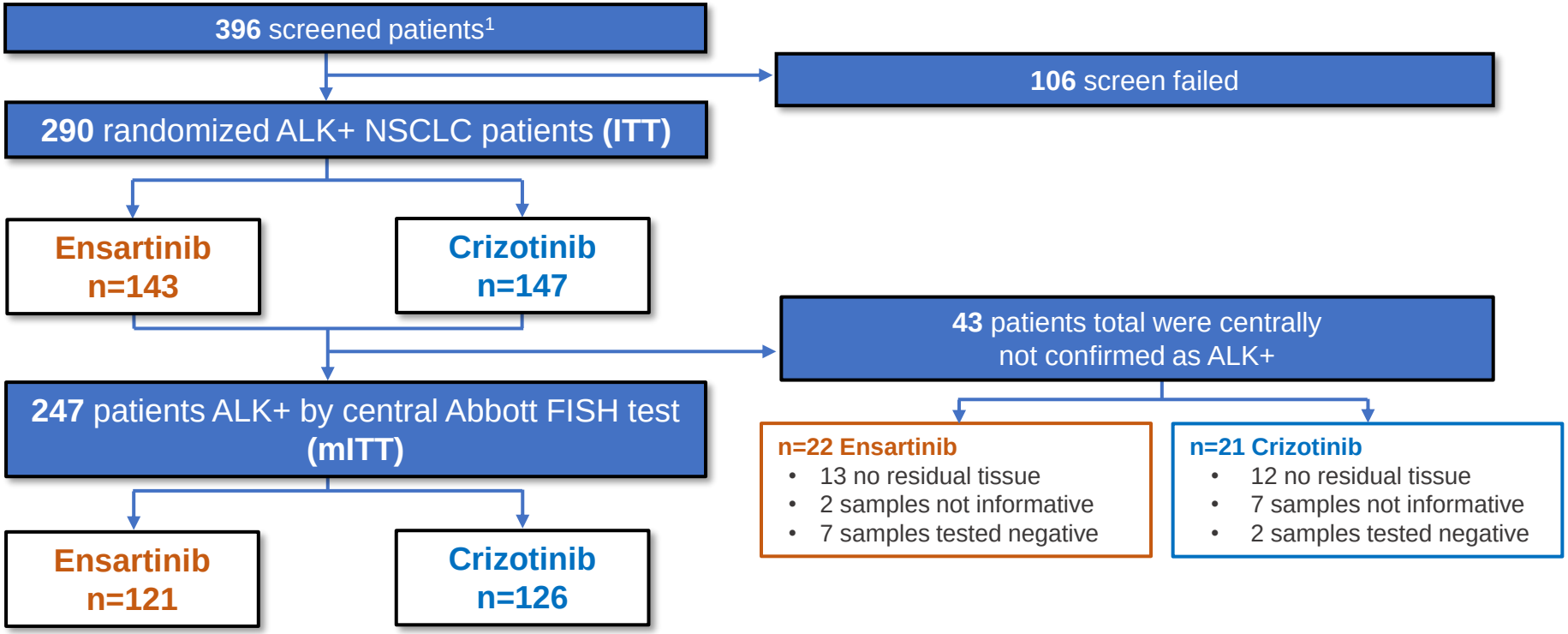
eXalt3: Global Phase 3, Open-Label, Randomized, Multicenter Study[1]



Primary endpoint: blinded independent review committee (BIRC)–assessed median PFS (mPFS) per RECIST v1.1 in ITT population
Key secondary endpoints: OS, ORR/DOR (overall and brain), TTF in the brain, QOL (EORTC, LCSS)

ALK, anaplastic lymphoma kinase; BID, twice daily; BL, baseline; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; FDA, US Food and Drug Administration; FISH, fluorescence in situ hybridization; ITT, intent to treat; LCSS, Lung Cancer Symptom Scale; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QOL, Quality of life; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROW, rest of world; TTF, time to treatment failure.

1. Selvaggi G, et al. *J Thoracic Oncol* 2020;15(suppl 10):E41-E42. Oral presentation at the 2020 WCLC virtual Presidential Symposium by L Horn.



ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; ITT, intent to treat; mITT, modified ITT; NSCLC, non-small cell lung cancer

1. Selvaggi G, et al. *J Thoracic Oncol* 2020;15(suppl 10):E41-E42. Oral presentation at the 2020 WCLC virtual Presidential Symposium by L Horn.

Study Summary from the 2020 WCLC Presidential Symposium[1]

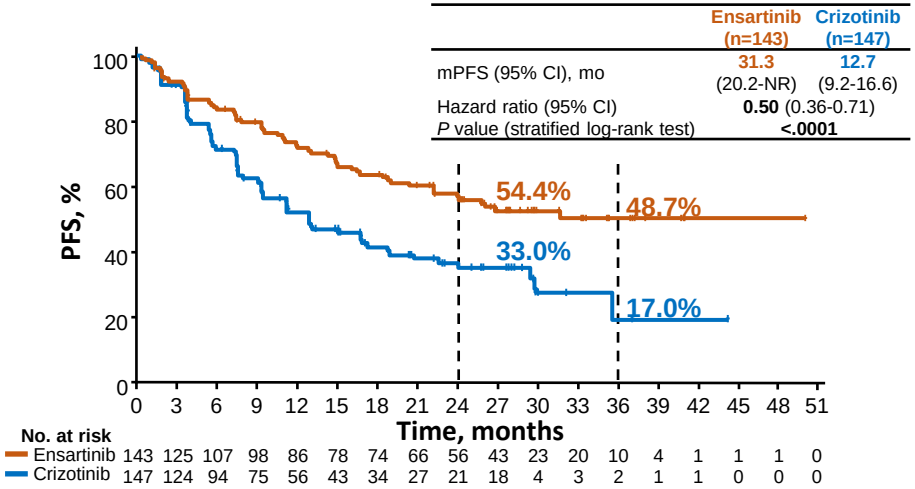
- An interim analysis was presented August 8, 2020, based on a database lock date of July 1, 2020
- In the ITT population, ensartinib achieved a median progression free survival (PFS) of 25.8 vs 12.7 months for crizotinib; HR, 0.51 (95% CI, 0.35-0.72); *P*=.0001
- In the modified ITT population (patients with centrally confirmed ALK+ NSCLC), median PFS with ensartinib was not reached vs 12.7 months for crizotinib; HR, 0.45 (95% CI, 0.30-0.66); *P*<.0001
- In the modified ITT population, median overall survival (OS) was not reached in either the ensartinib or crizotinib arm
  - 24-month OS for ensartinib was 77.9% vs 78.2% for crizotinib
- Ensartinib showed a favorable safety profile with low-grade rash and transaminitis as the most frequent treatment-related AEs
- **Here we present an update of efficacy based on a December 8, 2020, data cut, exploratory biomarker analyses, and quality of life (QOL) data**

AE, adverse event; ALK, anaplastic lymphoma kinase; HR, hazard ratio; ITT, intent to treat; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

1. Selvaggi G, et al. *J Thoracic Oncol* 2020;15(suppl 10):E41-E42. Oral presentation at the 2020 WCLC virtual Presidential Symposium by L Horn.

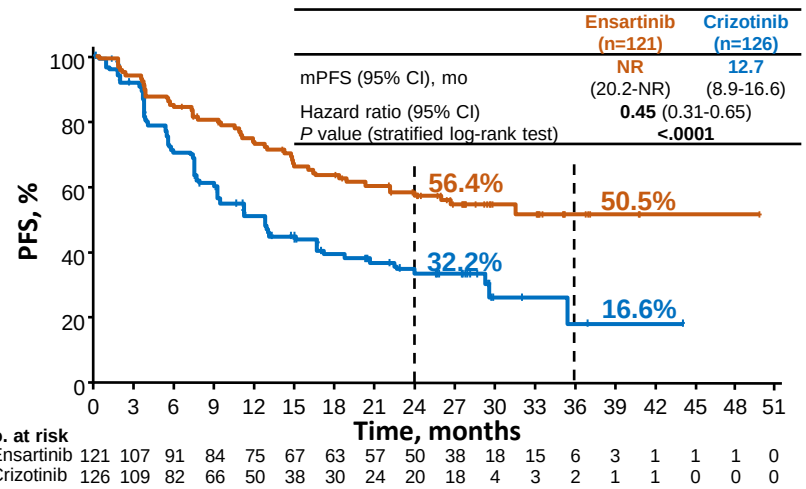
Updated PFS (December 8, 2020)

PFS per IRC, ITT Population



Median follow-up, mo	
Ensartinib	27.6
Crizotinib	21.9

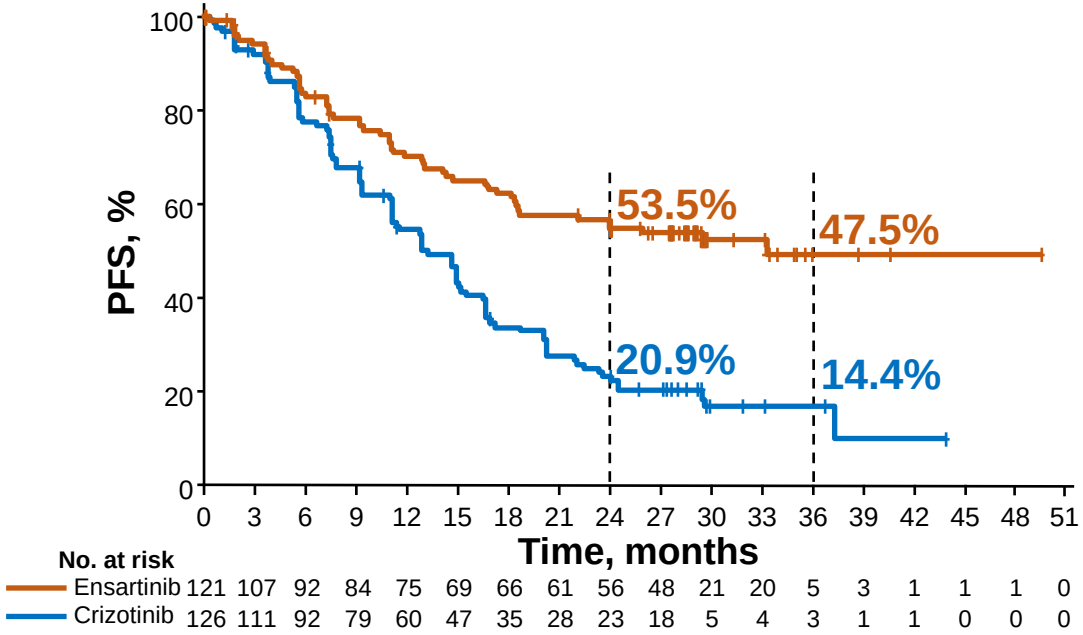
PFS per IRC, mITT Population



Median follow-up, mo	
Ensartinib	27.6
Crizotinib	22.8

IRC, independent reviewer committee; ITT, intent to treat; mITT, modified ITT; mPFS, median PFS; NR, not reached; PFS, progression-free survival.

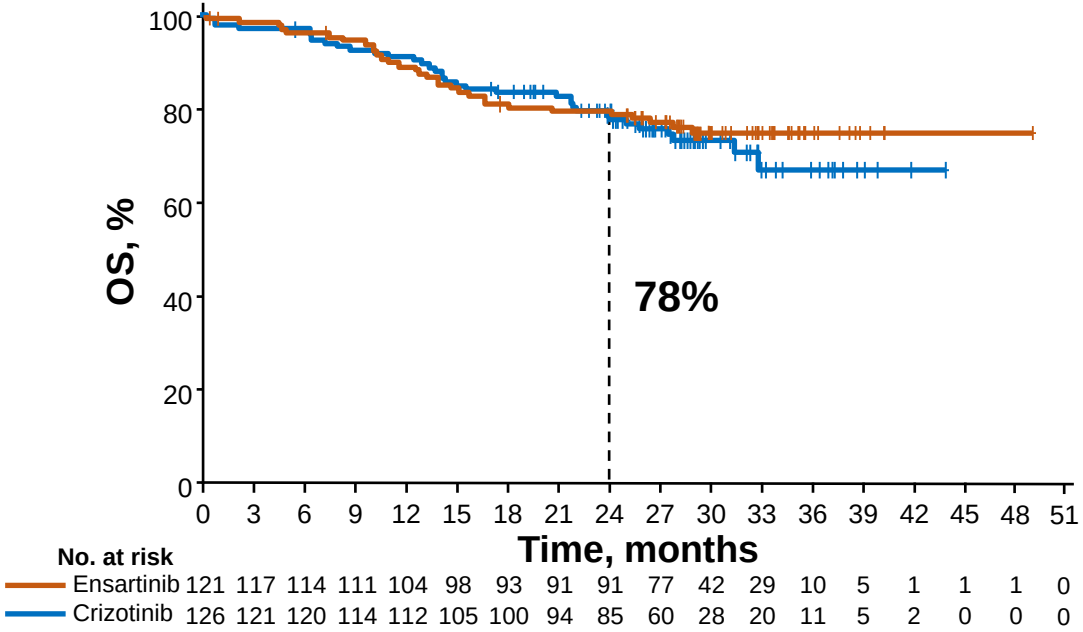
PFS by INV (mITT population, December 8, 2020)



	Ensartinib (n=121)	Crizotinib (n=126)
mPFS (95% CI), mo	33.2 (18.3-NR)	12.9 (11.0-15.0)
Hazard ratio (95% CI)	**0.45** (0.32-0.64)	
P value (log-rank test)	**<.0001**	

INV, investigator; mITT, modified intent to treat; mPFS, median PFS; NR, not reached; PFS, progression-free survival.

Updated OS (mITT population, December 8, 2020)



	Ensartinib (n=121)	Crizotinib (n=126)
mOS (95% CI), mo	NR (NR-NR)	NR (NR-NR)
Hazard ratio (95% CI)	**0.90** (0.55-1.49)	
P value (log-rank test)	**.695**	

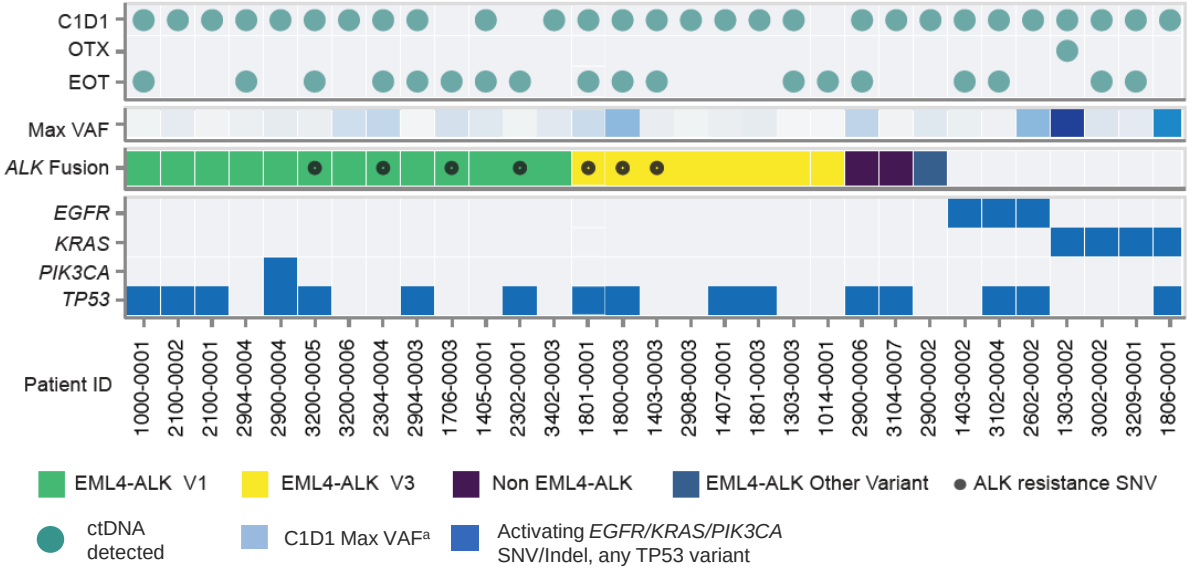
mOS, median OS; mITT, modified intent to treat; NR, not reached; OS, overall survival..

Methods: Biomarker Analyses

- Tumor tissue
  - Tissue obtained (archival, fresh biopsy) at study entry and post-treatment upon progression, if possible
- Circulating tumor DNA (ctDNA)
  - Approximately 20 mL of blood was collected pre-dose on cycle 1, day 1 and on day 1 of each cycle through the end of trial. Between 1 to 4 mL of plasma was processed for ctDNA analysis
- *ALK* variant types, maximum somatic variant allele frequency and co-occurring somatic variants in *EGFR*, *KRAS*, *PIK3CA*, and *TP53a* were evaluated using next-generation sequencing
  - Analyses were performed at a certified, College of American Pathologists–accredited, laboratory (Guardant Health, Inc)

Overview of Patient Mutational Profile Based on ctDNA

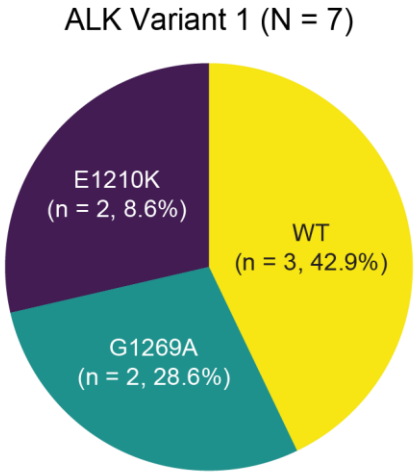
- *EML4-ALK* fusions were detected in 22 patients
  - 13 patients had variant type 1
  - 8 patients had variant type 3
  - 1 *EML4-ALK* fusion with no associated variant type was identified
- 7 patients without an *ALK* fusion had a driver mutation in *EGFR/KRAS*

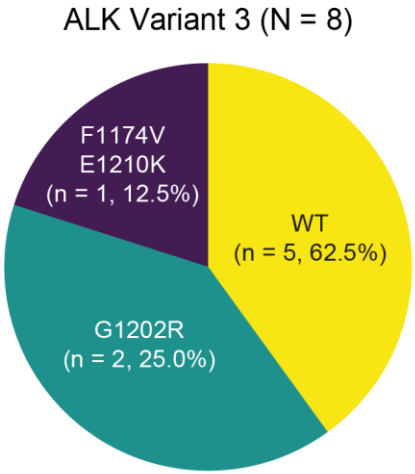


ALK, anaplastic lymphoma kinase; C1D1, cycle 1, day 1; ctDNA, circulating tumor DNA; EOT, end of trial; Max VAF, maximum somatic variant allele frequency; SNV, single-nucleotide variation; V, variant.
[a] Low VAF (white) to high VAF (dark blue, ≈50%).

ALK SNVs Detected in V1 and V3 Fusions at Disease Progression

- 7/15 (46.7%) patients with an ALK+ fusion detected at progression on ensartinib had an ALK resistance SNV
  - ALK resistance SNVs were acquired at EOT in 5/5 (100%) patients with both C1D1 and EOT timepoints
  - In patients with ALK V1, G1269A was detected in 2 patients, while 2 patients had E1210K mutations
  - G1202R was detected only in patients with ALK V3
  - Concurrent mutations, E1210K and F1174V, were detected in 1 patient with ALK V3





ALK, anaplastic lymphoma kinase; C1D1, cycle 1, day 1; EOT, end of trial; SNV, single-nucleotide variation; V, variant.

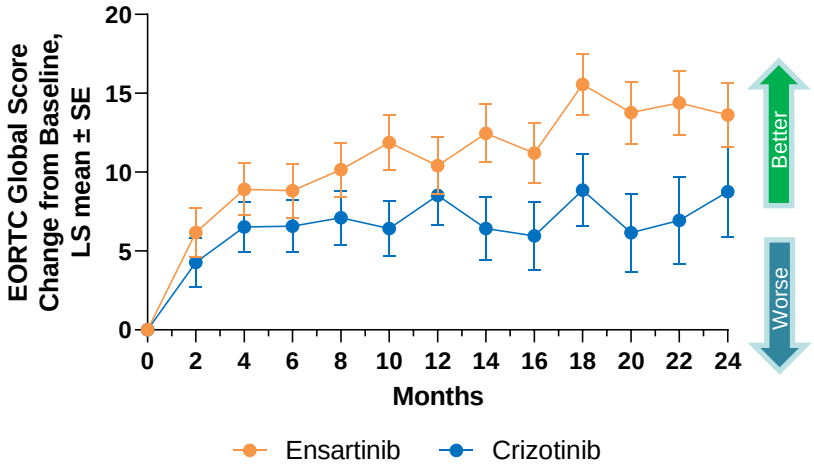
PRO: QOL Measures

- The **EORTC C30/LC13** QOL questionnaire is a health-related QOL instrument consisting of 13 items for use in lung cancer clinical trials; the patient assesses symptoms or problems experienced over the past week
  - EORTC C30/LC13 items were summarized by time point. *A higher score signifies a better QOL*
  - Time to deterioration (TTD) is defined at the time from date of randomization to a worsening of ≥10 points (on a 100-point scale) in each item score of the EORTC C30/LC13
- The **LCSS** is a QOL assessment designed for use in clinical trials in patients with lung cancer
  - Patients are asked to assess 6 symptoms and their effect on symptomatic distress, functional activities, and global quality of life on 9 visual analog scales
  - Results were summarized by time point. *A lower score signifies a better QOL*
  - TTD is defined as the time from date of randomization to a worsening of ≥15 points (on a 100-point scale) in each item score
- **Patients completed both QOL instruments at baseline, Day 1 (pre-dose), C2D1, C3D1, then approximately every 8 weeks (2 cycles), and at the End of Trial Treatment visit**

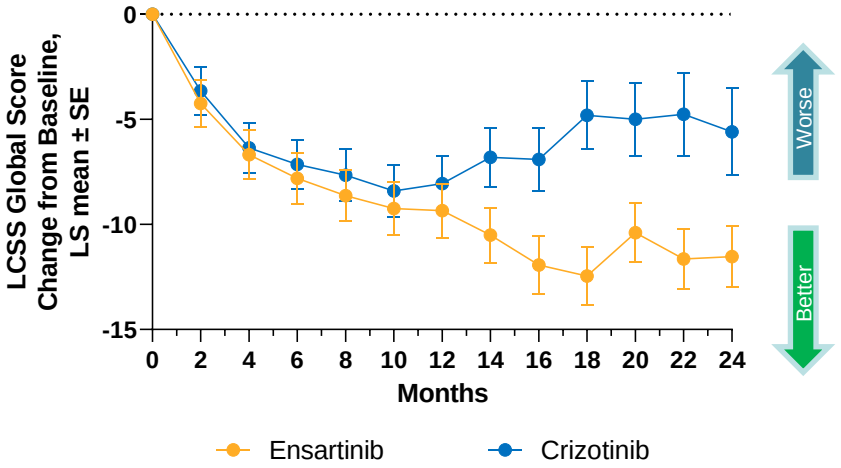
EORTC, European Organisation for Research and Treatment of Cancer; LCSS, Lung Cancer Symptom Scale; PRO, patient-reported outcome; QOL, quality of life.

QOL (ITT population)

Change from Baseline in EORTC



Change from Baseline in LCSS



- Patients treated with ensartinib had better QOL scores on both the EORTC and LCSS
- Benefit appeared to be maintained over time

EORTC, European Organisation for Research and Treatment of Cancer; LCSS, Lung Cancer Symptom Scale; LS, least squares; QOL, quality of life.

QOL (ITT population)

Time to Deterioration

	EORTC-C30/LC13		LCSS	
	Ensartinib n=143	Crizotinib n=147	Ensartinib n=143	Crizotinib n=147
Median TTD, months	22.2	15.9	NR	NR
95% CI	12.6-33.2	11.2-NR	NR-NR	36.9-NR
HR[a]	0.86		0.73	
95% CI	0.60-1.24		0.43-1.25	
P-value	0.419		0.253	

[a] HR estimate with covariates in Cox model.

TTD is defined as the time from date of randomization to a worsening of at least 10 points (on a 100-point scale) in each item score of the EORTC C30/LC13 and of at least 15 points (on a 100-point scale) in each item score of the LCSS

EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; LCSS, Lung Cancer Symptom Scale; TTD, time to deterioration.

Conclusions

- This is an update of the eXalt3 phase III trial of ensartinib vs crizotinib based on an additional 5 months follow-up since the readout of the preplanned interim analysis on July 1, 2020
- As of December 8, 2020, median PFS by IRC of ensartinib reached 31.3 months in the ITT population and median PFS by INV of ensartinib reached 33.2 months in the mITT population with a 27.6-month median follow-up
- The favorable trend of OS is confirmed with a 2-year OS rate of 78% although analysis remains immature
- Exploratory biomarkers analysis showed a distinct resistance profile for ensartinib, with emerging E1210K and G1269A mutations and less frequent G1202R mutations (seen only in V3 cases) as detected using NGS on ctDNA at progression
- Patient-reported outcome measures showed improved QOL and a longer time to QOL deterioration in ensartinib- vs crizotinib-treated patients
- Finally, updated efficacy data confirm that ensartinib represents a new therapeutic option in the first-line setting for patients with ALK+ NSCLC

ALK, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA; INV, investigator; IRC, independent review committee; ITT, intent to treat; mITT, modified ITT; mPFS, median PFS; NGS, next-generation sequencing; non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QOL, quality of life; V, variant.

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eXalt3 Study

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